Benzodiazepine Tranquilizers and the Risk of Accidental Injury

GERRY OSTER, PHD, DANIEL M. HUSE, MA, SHELLEY F. ADAMS, MPA,
JOSEPH IMBIMBO, BA, AND MASON W. RUSSELL, MAPE

Abstract: To determine whether benzodiazepine tranquilizers increase the risk of accidental injury requiring medical attention, we used pharmacy claims submitted to a large third-party payer to identify 4,554 persons who had been prescribed these agents and a matched control group of 13,662 persons who had been prescribed drugs other than benzodiazepines. We then used diagnoses recorded on claims submitted by medical care providers to identify all accident-related care received by these persons during three months before their first-observed prescription for a benzodiazepine or nonbenzodiazepine agent, respectively, and six months subsequently. We found accident-related care was more likely among persons who had been prescribed benzodiazepines; among these persons, the probability of an accident-related medical encounter was higher during months in which a prescription for a benzodiazepine had recently been filled compared to other months; and persons who had filled three or more prescriptions for these agents in the six months following initiation of therapy had a significantly higher risk of an accident-related medical event than those who had filled only one such prescription. Approximately two-fold risks of accident-related care were found, after controlling for age, sex, and prior utilization. (*Am J Public Health* 1990; 80:1467–1470.)

Introduction

Benzodiazepine tranquilizers were introduced in the United States in 1962 and rapidly supplanted barbiturates as anxiolytic agents of first choice. While they are among the most widely prescribed classes of drugs, there is mounting evidence that their use impairs cognitive performance and psychomotor skills. Persons given benzodiazepines have been found to perform poorly in driving simulator tests relative to those receiving placebo.[1,2] In addition, several forensic studies[3–6] have found a greater than expected number of benzodiazepine users among persons fatally injured in motor vehicle accidents.

Three epidemiologic investigations of impairment related to the use of minor tranquilizers have been reported to date. A study conducted in England over a two-year period found that patients receiving benzodiazepines and other minor tranquilizers were nearly five times more likely to experience a serious motor vehicle accident than those who had not used these drugs.[7] Another study examined persons hospitalized for injuries resulting from a motor vehicle accident and found that persons identified as drivers who were at fault in their accidents were somewhat more likely to have filled a prescription for hypnotics or tranquilizers during the three-month period prior to the accident than those identified as passengers.[8]

The third epidemiologic investigation, a retrospective cohort study using claims data from a large health insurer,[9] compared accident-related medical care among persons who were prescribed benzodiazepines with that of a matched control group who had not been prescribed these agents. Persons prescribed benzodiazepines were more likely to have accident-related care, but also were reported to experience a greater number of nonaccident-related medical encounters, suggesting differences in care-seeking behavior rather than risk of accidental injury. Without data on medical utilization prior to therapy, the effect of differences in care-seeking behavior could not be determined.

To circumvent this difficulty, in the present study we employ a pretest-posttest design[10] to examine three key questions: 1) Are persons who are prescribed benzodiazepine tranquilizers more likely to require accident-related medical care? 2) Is there evidence of a temporal relation between prescriptions for these agents and the likelihood of an accident-related medical encounter? 3) Is there evidence of a relation between the number of such prescriptions and the risk of these encounters?

Methods

Data Source

Data for this study were obtained from the health care claims processing system of Master Health Plus™, a health insurance plan operated by Blue Cross and Blue Shield of Massachusetts with a membership in excess of one million persons. Plan members receive first-dollar coverage for physician services, inpatient and outpatient care, and prescription drugs, with a $5 copayment for provider services, a $4 copayment for prescription drugs ($3 for generics), and a $500 annual limit on reimbursement for mental health services. All claims for care are provider-submitted, and nondrug claims contain detailed diagnostic information in the form of physician-recorded ICD-9-CM codes. A complete record of medical utilization may be compiled for each plan member during his or her period of enrollment.

To be eligible for inclusion in the present study, members had to be enrolled continuously in the plan during the period April 1986–September 1987. Persons over 65 years of age or otherwise eligible for Medicare benefits were excluded from the study because Medicare claims were not available.

For our sample of persons who were prescribed benzodiazepines (benzodiazepine "users"), we selected all eligible plan members who had at least one pharmacy claim for a benzodiazepine tranquilizer (alprazolam, chlordiazepoxide, clorazepate, diazepam, lorazepam, or oxazepam, either singly or in combination with any other agent) during July 1986–March 1987, and had no claims for any of these agents between April 1986–June 1986. We considered the date of the first-observed pharmacy claim for a benzodiazepine agent to be the date of initiation of benzodiazepine therapy. A total of 4,554 benzodiazepine users were identified and included in the study.

From Policy Analysis Inc. (Oster, Huse, Russell); New England Institute for Healthcare Services Research (Adams); and Electronic Data Systems, Inc. (Imbimbo). Address reprint requests to Gerry Oster, PhD, Policy Analysis Inc., 1577 Beacon Street, Brookline, MA 02146. This paper, submitted to the Journal July 11, 1989, was revised and accepted for publication April 17, 1990.

Three persons who were not prescribed benzodiazepines (benzodiazepine "nonusers") were matched randomly to each user. Nonusers were selected from among those eligible patients who had no pharmacy claims for a benzodiazepine tranquilizer between April 1986–March 1987, were not related by blood or marriage to any patient who had a claim for such an agent during April 1986–March 1987, and had at least one claim for a nonbenzodiazepine agent during July 1986–March 1987. We considered the date of the first-observed nonbenzodiazepine drug claim to be the date of therapy initiation for each nonuser, and we matched nonusers to users on the basis of age, sex, and the calendar month during which therapy was initiated.

For each person in the sample, we then compiled all health care claims for three months prior to the date of initiation of therapy, and for six months subsequent to that date. Every nondrug claim was classified as either accident- or nonaccident-related on the basis of the physician-recorded ICD-9-CM diagnosis codes. Claims with any ICD-9-CM diagnosis code between 800-959 or 990-995 were considered to be accident-related; all other claims were considered nonaccident-related. Emergency visits were identified on the basis of accompanying information noting the type of service rendered (i.e., "emergency medical care").

Univariate Analysis

To examine the relation between benzodiazepine use and overall risk of accidental injury, we considered three outcomes: 1) the occurrence of any accident-related *emergency outpatient visit;* 2) the occurrence of any accident-related *hospital admission;* and 3) the occurrence of an accident-related *medical encounter of any type*. The frequencies of these events among benzodiazepine users and nonusers during the six-month period following initiation of therapy were determined.

To examine evidence of a temporal relationship between benzodiazepine use and risk of accidental injury, among users we compared the frequencies of accident-related medical encounters during months of presumed drug exposure to those during months of presumed nonexposure. A user was presumed to have been "exposed" to benzodiazepines during a given month if a pharmacy claim for one of these agents was observed in that month or the previous month.

Finally, to ascertain whether there is evidence of a relation between the number of benzodiazepine prescriptions filled and the risk of accidental injury, we compared rates of accident-related medical events among users according to their numbers of pharmacy claims for benzodiazepine agents during the six months following initiation of therapy. Two groups of users were defined—those who had only one pharmacy claim for a benzodiazepine agent and those who had three or more such claims—and we compared rates of accident-related medical events between them.

Comparisons of rates were expressed as ratios, or relative risks, and 95 percent confidence intervals were calculated by the Taylor-series method.[11]

Multivariate Analysis

To control for factors other than benzodiazepine use, we fitted a Cox proportional hazards model[12] and included as covariates age, sex, and the logarithms of total accident- and nonaccident-related medical care charges during the three months prior to therapy.

We used a similar proportional hazards model to compare the risk of accident-related medical encounters during months in which a user was presumed to have been exposed to benzodiazepines to all other months. Included in this model were a set of additional binary variables indicating, for each month during the six-month period of follow-up, whether a user was presumed to have been exposed to benzodiazepines in that month.

Finally, we used a similar model to compare outcomes between benzodiazepine users who filled three or more prescriptions for these agents and those who filled only one such prescription. Risks of each accident-related event were estimated as a function of the number of benzodiazepine prescriptions filled, age, sex, and the logarithms of total accident- and nonaccident-related medical-care charges during the three months prior to therapy.

Results

Profile of Benzodiazepine Users and Patterns of Benzodiazepine Use

Benzodiazepine users were more likely to be women than men (65.4 percent versus 34.6 percent), and more than one-half (53.5 percent) were less than 45 years of age. Approximately one-half (48.3 percent) of benzodiazepine users filled only a single prescription for one of these agents, 21.3 percent filled two prescriptions, 11.2 percent filled three prescriptions, and 19.2 percent filled four or more prescriptions over the six-month period of follow-up.

During the three-month period prior to the initiation of therapy, benzodiazepine users were twice as likely as nonusers (95 percent CI: .96, 4.44) to have at least one accident-related emergency outpatient visit (2.4 versus 1.2 per 1,000); 1.7 times as likely (95 percent CI: 1.11, 2.61) to have an accident-related hospital admission (7.2 versus 4.2 per 1,000); and 1.5 times as likely (95 percent CI: 1.29, 1.66) to have an accident-related medical encounter of any type (73.6 versus 50.2 per 1,000.

Accident-Related Care among Benzodiazepine Users and Nonusers

During the six-month period following the initiation of therapy, benzodiazepine users were significantly more likely than nonusers to require accident-related care (Table 1). Compared to nonusers, users were more than twice as likely to have had an accident-related emergency outpatient visit, about 1.6 times more likely to have experienced at least one accident-related hospital admission, and approximately 1.2 times more likely to have had at least one accident-related medical encounter of any type.

We examined rates of accident-related encounters among persons who had no accident-related care during the three-month period prior to the initiation of therapy. Unadjusted relative risks of accident-related events among benzodiazepine users were similar to those reported in Table 1.

TABLE 1—Risks of Accident-related Medical Encounters among Persons Who Were Prescribed Benzodiazepine Tranquilizers ("users") Compared to Those Who Were Not ("nonusers")

Accident-Related Medical Encounter	Monthly Rate per 1,000		Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk* (95% CI)
	Users	Nonusers		
Any emergency outpatient care	1.06	.49	2.16 (1.35,3.50)	2.09 (1.27,3.42)
Any hospital admission	1.39	.88	1.58 (1.07,2.34)	1.27 (.84,1.90)
Any medical encounter	23.31	18.84	1.24 (1.14,1.35)	1.15 (1.05,1.26)

*Hazard ratio adjusted for age, sex, and pretreatment medical care utilization.

For emergency outpatient visits, the unadjusted relative risk was 2.18 (95 percent CI: 1.27, 3.77); for hospital admissions, it was 1.77 (95 percent CI: 1.13, 2.78); and for medical encounters of any type, it was 1.21 (95 percent CI: 1.10, 1.33). Controlling for age, sex, and health care utilization in the three months prior to the initiation of therapy did not change the excess risk of accident-related medical encounters among benzodiazepine users relative to nonusers appreciably (Table 1).

Accident-Related Care by Temporal Pattern of Benzodiazepine Use

Outcomes among benzodiazepine users were examined during 11,389 months of presumed drug exposure (i.e., months in which prescriptions for benzodiazepines had recently been filled) and 15,935 months in which they were presumed unexposed. A greater likelihood of accident-related medical encounters was observed during months of exposure (Table 2). Controlling for age, sex, and health care utilization in the three months prior to treatment, adjusted relative risks were somewhat lower than unadjusted ratios but remained excessive.

Accident-Related Care by Amount of Benzodiazepine Use

Benzodiazepine users who filled at least three prescriptions for these agents (n = 1,384) were more likely to have required accident-related care than those who filled only one such prescription (n = 2,200) (Table 3). Compared to users who filled one prescription, those who filled three or more prescriptions were about 2.4 times more likely to have had an accident-related emergency outpatient visit, and roughly 1.3 times more likely to have had an accident-related medical encounter of any type. The relative risk of an accident-related hospital admission was 1.5. Controlling for age, sex, and health care utilization during the three-month period prior to treatment did not change these risks substantially (Table 3).

Discussion

The results of this study suggest that the use of benzodiazepine tranquilizers increases the risk of accidental injury requiring medical attention. Emergency outpatient care, hospital admissions, and medical encounters of all types were more frequent among persons who were prescribed benzodiazepines than those who were not; among persons who were prescribed benzodiazepines, the likelihood of such care was higher during months in which such a prescription had recently been filled than during other months; and persons who filled three or more prescriptions for benzodiazepines over a six-month period had greater numbers of accident-related medical encounters than those who had filled only one such prescription. Increased risks of accident-related care remain even after controlling for the potentially confounding effects of age, sex, and prior differences in utilization.

TABLE 2—Risks of Accident-Related Medical Encounters among Persons Who Were Prescribed Benzodiazepine Tranquilizers during Months in Which Such a Prescription Was Recently Filled ("exposed") Compared to other Months ("unexposed")

Accident-Related Medical Encounter	Monthly Rate per 1,000		Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk* (95% CI)
	Exposed	Unexposed		
Any emergency outpatient care	1.23	.94	1.31 (.63,2.70)	1.13 (.46,2.77)
Any hospital admission	1.84	1.07	1.73 (.91,3.27)	1.42 (.66,3.04)
Any medical encounter	31.87	17.19	1.85 (1.59,2.16)	1.28 (1.04,1.56)

*Hazard ratio adjusted for age, sex, and pretreatment medical care utilization.

TABLE 3—Risks of Accident-related Medical Encounters among Persons Who Filled Three or more Prescriptions for Benzodiazepine Tranquilizers ("scripts") Compared to Those Who Filled one such Prescription

Accident-Related Medical Encounter	Monthly Rate per 1,000		Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk* (95% CI)
	Three or More Scripts	One Script		
Any emergency outpatient care	1.81	.76	2.38 (1.16,6.04)	2.64 (1.15,6.04)
Any hospital admission	1.57	1.06	1.48 (.70,3.13)	1.42 (.67,3.03)
Any medical encounter	27.70	21.52	1.29 (1.10,1.51)	1.30 (1.09,1.55)

*Hazard ratio adjusted for age, sex, and pretreatment medical care utilization.

We note that approximately one-third of the benzodiazepine users in our sample filled three or more prescriptions for these agents over a six-month period, and that these persons were at highest risk. Compared to persons who were not prescribed benzodiazepines, persons who filled three or more such prescriptions were 3.7 times (95 percent CI: 2.05, 6.68) more likely to have had an accident-related emergency outpatient visit (10.8 versus 2.9 per 1,000), 1.8 times (95 percent CI: 0.99, 3.21) more likely to have had an accident-related hospital admission (9.4 versus 5.3 per 1,000), and 1.5 times (95 percent CI: 1.30, 1.67) more likely to have had at least one accident-related medical encounter of any type (166.2 versus 113.0 per 1,000).

Our control group consisted of patients who received prescription drugs other than benzodiazepines, some of which may also affect the central nervous system. Our findings concerning the increase in risk of accidental injury associated with the use of benzodiazepines may therefore be conservative. Since we do not know whether persons who filled prescriptions for benzodiazepines in fact took any medication and, if so, how much they took and for how long, we may have overestimated drug exposure in our user group. Similarly, there may have been some exposure to these agents among our nonusers. While we excluded all persons with pharmacy claims for benzodiazepines from our nonuser group as well as those related by blood or marriage to these persons, we could not exclude those who had received these agents directly from their physician or those who had obtained these drugs illicitly. Our estimates of relative risk may therefore be conservative.

We considered the possibility that benzodiazepine users simply may be more accident prone than nonusers, due to differences in behavior, lifestyle, occupation, and so forth. We feel that this is unlikely, however; such factors could not account for the *temporal* association between benzodiazepine use and accident-related care that we observed among patients receiving these agents.

Since benzodiazepine tranquilizers often are prescribed for acute anxiety, we also considered the possibility that anxiety itself rather than the prescribed medication may cause users of these agents to be more accident-prone. Accordingly, we identified all persons who had claims for

mental health services at any time during the 30 days prior to or following the initiation of benzodiazepine or nonbenzodiazepine therapy, but no such claims previously. When included as a covariate in our proportional hazards model, however, this variable was found to be uncorrelated with patients' risk of accident-related care, and was subsequently dropped. We note also that the results of controlled experiments lend credence to our finding that benzodiazepine use per se increases the risk of accident-related care.

We also considered the possibility that benzodiazepine users simply may be more likely than nonusers to seek medical treatment for minor injuries. Benzodiazepine users have been found to have higher rates of medical encounters unrelated to accidents than nonusers,[8] which suggests that users might be prone to seek professional care more often than nonusers. Again, the temporal association between the filling of prescriptions for benzodiazepines and accident-related encounters cannot readily be explained by differences in care-seeking behavior. Also, the excess in accident-related care among persons who received such prescriptions relative to those who did not remained even after we controlled for prior differences in patterns of health care utilization. Finally, while a greater number of outpatient visits might be related to differences in propensity to seek care, an excess of accident-related hospital admissions among benzodiazepine users can less plausibly be attributed to patients' discretion.

The foremost limitation of our study is that we could observe neither benzodiazepine use nor the occurrence of accidental injuries directly. We inferred the former from the presence in patients' records of pharmacy claims for these agents. We inferred the latter from the presence of nondrug claims with physician-recorded ICD-9-CM diagnosis codes indicating injury as the reason for rendering care, and the assumption that such injuries were accidental and not self-inflicted. To the extent that plan members may have received prescription drugs from other sources, we may have incorrectly identified some persons as nonusers who in fact used benzodiazepines. While it is also possible that some study subjects were treated for injuries without corresponding claims being submitted to the plan, we believe that this is unlikely. Also, there is no apparent reason why such out-of-plan care should be more frequent among persons who were prescribed benzodiazepines than among those who were not, or vice versa.

A more likely problem deriving from the use of claims data is that some of the accident-related care that we observed in the six-month period following initiation of therapy may in fact have been for follow-up treatment of injuries that occurred prior to therapy. The benzodiazepine user group, for example, may have included persons with pre-existing back strain, for which benzodiazepines are sometimes prescribed. Similarly, the benzodiazepine nonuser group, which was selected from among all persons with nonbenzodiazepine drug claims, may have included patients who were prescribed analgesics for control of prior accident-related pain. We note, though, that when we compared rates of accident-related encounters among persons who had no such care during the three-month period prior to therapy, our results were largely unchanged.

There are important limitations inherent in any study that uses claims data. We note, however, that data bases of the type we have employed are being used increasingly to study outcomes of care: health care claims data, for example, recently have been used to monitor the incidence of birth defects among patients receiving the acne medication, isotretinoin,[13] and to estimate the risks of mortality and reoperation following prostatectomy.[14]

Despite possible limitations, we believe that our study has several important implications. Our findings suggest that the use of benzodiazepine tranquilizers may increase the risk of accidental injury. They therefore corroborate those of previous studies. The conditions for which these agents are prescribed, however, need and deserve treatment. Accordingly, patients should be advised of the potential risks associated with the use of these agents. Also, when appropriate, alternative therapies might be considered, particularly for persons who must operate machinery or a motor vehicle, those who would use alcohol, and those who may require an extended period of therapy.

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